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Running title: Pregnancy outcomes and $PM_{2.5}$ in a national study

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Abstract

Background: Numerous studies have examined associations between air pollution and pregnancy outcomes but most have been restricted to urban populations living near monitors.

Objectives: To examine the association between pregnancy outcomes and fine particulate matter in a large national study including urban and rural areas.

Methods: Analyses were based on approximately 3 million singleton live births in Canada between 1999 and 2008. Exposures to $PM_{2.5}$ (particles of median aerodynamic diameter < 2.5 μm) were assigned by mapping the mother's postal code to a monthly surface based on a national land use regression model that incorporated observations from fixed-site monitoring stations and satellite-derived estimates of $PM_{2.5}$. Generalized estimating equations were used to examine the association between $PM_{2.5}$ and preterm birth (gestational age < 37 weeks), term low birth weight (<2500 g), small for gestational age (SGA, <10th percentile of birth weight for gestational age), and term birth weight, adjusting for individual covariates and neighbourhood socioeconomic status (SES).

Results: In fully adjusted models, a 10 $\mu g/m^3$ increase in $PM_{2.5}$ over the entire pregnancy was associated with SGA (OR = 1.04, 95% CI 1.01, 1.07) and reduced term birth weight (-20.5 g, 95% CI -24.7, -16.4). Associations varied across subgroups based on maternal place of birth and period (1999-2003 vs. 2004-2008).

Conclusions: This study based on approximately 3 million births across Canada and employing $PM_{2.5}$ estimates from a national spatiotemporal model provides further evidence linking $PM_{2.5}$ and pregnancy outcomes.

Introduction

Numerous studies have examined the association between air pollution and pregnancy outcomes. Meta-analyses and pooled multi-centre analyses suggest that particulate matter is associated with low birth weight and preterm birth, although there is heterogeneity among centres (Dadvand et al. 2013; Stieb et al. 2012). Most studies have been based on exposure estimates from fixed-site monitoring data, and therefore have been restricted to urban populations living in the vicinity of monitoring stations (Stieb et al. 2012). However, population coverage of ground based monitoring is low; Guay et al. (2010) found that the proportion of National Population Health Survey participants in Canada living in a census subdivision containing an air pollution monitor was at best 41% among the various pollutants considered. Estimates of particulate matter concentrations from models and/or satellite observations have made it possible to extend analyses of effects to large national studies comprising both urban and rural areas (Crouse et al. 2012; Lim et al. 2012). To this point, however, few analyses have been reported of model/ satellite-based exposure estimates and pregnancy outcomes (Fleischer et al. 2014; Hyder et al. 2014; Kloog et al. 2012).

In this paper we employ estimates of fine particulate matter (median aerodynamic diameter < 2.5 μm, $PM_{2.5}$) from a spatiotemporal model using ground measurements and satellite-based estimates and apply these to approximately 3 million births across Canada between 1999 and 2008. We examined preterm birth, term low birth weight, and small for gestational age as binary variables, and term birth weight as a continuous variable.

Methods

Pregnancy Outcome Data

Data on all singleton live births between 1999 and 2008 were accessed through Statistics Canada (Statistics Canada 2015a) after obtaining approval from Health Canada's Research Ethics Board. Birth records included data on infant sex, date of birth, gestational age, birth weight, birth order, number of stillborn (if multiple birth), postal code of maternal place of residence at child's birth, maternal age at child's birth, marital status, total number of liveborn and stillborn (ever), province/country of mother and father's birth, and mother's education level in years (Quebec only). Data on maternal behaviours including smoking and alcohol consumption were not available. Pregnancy outcomes under study were preterm birth (gestational age < 37 weeks), term low birth weight (LBW, <2500 g), small for gestational age (SGA, <10 percentile of birth weight for gestational age) (Kramer et al. 2001), and term birth weight as a continuous variable.

Geocoding and Socioeconomic Status

The Postal Code Conversion File Plus (PCCF+) was used to geocode birth records using the maternal postal code in order to obtain Statistics Canada standard geographic identifiers (Wilkins and Peters 2012). In urban Canada (75-80% of the population), postal codes generally refer to a small geographic area containing on average 30 people. Each postal code is represented spatially by a representative point or points. In urban areas, it is most often located at the mid-point along a block-face portion which generally corresponds to one side of a road. For apartment buildings it is often the location of the building. For rural Canada, postal codes can cover a large geographic area with as many as 1,100 people, encompassing more than one census dissemination area. For these cases, postal code representative points are randomly allocated using a population-weighted file from Statistics Canada (Statistics Canada 2013), such that the probability of a given dissemination area (DA) centroid being used reflects the spatial distribution of the underlying population. Postal codes were considered rural if the second character was zero. Using geocoded birth records, neighbourhood-level socioeconomic status variables were calculated at the DA level using census data, including proportion of individuals aged 15 and over who were unemployed, proportion of individuals aged 15 and over in the lowest income quintile, and proportion of females aged 25 and over with post-secondary education (Crouse et al. 2012; Dadvand et al. 2013). Variables were calculated based on the census closest to the date of birth (2001 or 2006) (Statistics Canada 2015b). There were 52,993 and 54,626 dissemination areas in the 2001 and 2006 censuses respectively, each with a population of approximately 400-700 people.

$PM_{2.5}$ Data

$PM_{2.5}$ exposures were assigned by mapping the mother's six-character postal code to a monthly surface based on a North American land use regression model that incorporated observations from fixed-site monitoring stations and satellite-derived estimates of $PM_{2.5}$. Exposures were estimated for the entire duration of pregnancy, by trimester, and by gestational month.

Using the same two-stage methods as those described in Beckerman et al. (2013), a predictive spatiotemporal exposure model for ambient $PM_{2.5}$ was created for Canada by combining observed $PM_{2.5}$ levels with observations from the contiguous United States. These observations were combined to help stabilize the variability likely to be predicted by the small Canadian dataset. In Canada, there were 241 sites over a very large landmass while the U.S. dataset had a total of 1464 sites. There was a concern that the limited density of observations in Canada would reduce our ability to generate defensible predictive estimates. Given the adjacency of the observations in the U.S., it was determined that they could bolster the predictive capacity of a Canadian model.

During the first stage of modeling, a machine learning method, known as the Deletion/Substitution/Addition (DSA) algorithm, was implemented to create a land use regression (LUR) model, as described in Beckerman et al. (2013). Variables describing square of open (undeveloped) space within 200 meters of a location and $PM_{2.5}$ concentration estimated from remote sensing (squared and cubed) were chosen by the DSA algorithm for the LUR model as the most predictive variables using cross-validation selection techniques. Additionally, an indicator for the Canadian dataset was interacted with the remote sensing variable to provide a small marginal adjustment to the remote sensing contribution to the prediction. The polynomial terms served to reduce bias in the remote sensing estimates because they did not use any ground data to calibrate the predicted levels. The polynomial term on open space was selected by DSA because it predicted best and described the functional form of the relationship with observed $PM_{2.5}$ levels. The prediction results were very similar to those reported in Beckerman et al. (2013) (see Supplemental Material, Table S1). For Canada, the LUR model described 59% of the observed variability in the mean as measured by the cross-validated (CV) normalized pseudo-R2 based on v-fold cross-validated prediction error. However, there was significant residual variability as the non-normalized CV pseudo-R2 was 26%. In the second stage, the Bayesian Maximum Entropy interpolation method (Christakos, 1990) was used to create a spatiotemporal prediction model of the space-time residuals from the LUR model that were added to the LUR prediction estimates. This method (described in more detail in Beckerman et al. 2013), produced a final model with a CV R2 of 0.36. CV estimates were based on 1436 (10%) randomly selected leave-out observations from 22 monitoring sites. This model appeared less predictive than the US model (CV R2 = 0.79), however the poor fit was partly driven by a small number of outlying observations (see Supplemental Material, Figure S1), and removing them improved the model prediction (CV R2 = 0.53).

As a sensitivity analysis, we also employed monthly average concentrations from ground-based monitors for 24 cities with at least 85% complete monthly data. The total population of these cities based on the 2006 census was approximately 11,500,000, or about one third of the Canadian population.

Statistical Analysis

We used a similar approach to that employed in the recent International Collaboration on Air Pollution and Pregnancy Outcomes (ICAPPO) multi centre analysis (Dadvand et al. 2013), reporting unadjusted results, and incrementally adding adjustments for socioeconomic status, and maternal and infant characteristics. Generalized estimating equations (GEE) were used to examine the association between air pollution and preterm birth, term LBW, SGA and term birth weight, adjusting for covariates including infant sex, gestational age, parental age and marital status, parity, urban/ rural place of residence, place of birth of parents (within/outside Canada), season (winter (January to March), spring (April to June), summer (July to September) and fall (October to December)), year of birth and DA proportions of individuals aged 15 and over who were unemployed, of individuals aged 15 and over in the lowest income quintile, of females aged 25 and over with post-secondary education and of individuals who were visible minority. Visible minority groups are those defined by the Canadian Employment Equity Act and classification of individuals is based on response to census questions pertaining to self-identified population and aboriginal group (Statistics Canada 2015c). Because some provinces and territories had few births, we adjusted for location of mother's place of residence based on six regional airsheds (see Supplemental Material, Figure S2) (Personal communication, Dr. Jeffrey Brook, Environment Canada). We accounted for clustering of observations by DA by treating births from the same DA as repeated subjects in the GEE analysis.Subgroup analyses were conducted based on maternal place of birth (within vs. outside Canada), urban vs. rural place of residence, neighbourhood socioeconomic status, and study period (1999-2003, 2004-2008). Results were considered statistically significant if p-value<0.05. All analyses were conducted using SAS version 9.3.

Results

During the study period there were 3,104,090 live births. Of these, 3,061,155 (98.6%) could be mapped to $PM_{2.5}$ exposures, of which 2,969,380 were singletons (in accordance with Statistics Canada disclosure rules, all frequencies were randomly rounded to base five). After further excluding births with missing covariate data, analyses of preterm birth, term LBW and birth weight, and SGA were based on up to 2,966,705; 2,781,940 and 2,965,440 births respectively. The overall prevalence of preterm birth was 6.23 percent, of term LBW, 1.57 percent and SGA, 8.31 percent. Mean assigned $PM_{2.5}$ exposure over the entire pregnancy was 8.4 μg/m^3 and interquartile range (IQR) was 3.6 μg/m^3 (Table 1). Mean exposures by trimester and month were similar, but there was somewhat greater variability compared to exposure over the entire pregnancy reflected by greater standard deviations and interquartile ranges. Entire pregnancy exposures were highly correlated with trimester and monthly exposure periods (Spearman's r = 0.85–0.91 and 0.74–0.83, respectively) (see Supplemental Material, Table S2). Prevalence of each outcome and mean $PM_{2.5}$ exposure by infant, maternal and neighbourhood characteristics are shown in Table 2. Appreciable differences in both outcome prevalence and exposure were noted by infant, maternal and neighbourhood characteristics. In particular, there was a time trend of reduced $PM_{2.5}$, but not of pregnancy outcome, between 1999 and 2008. There was also a consistent trend of increased prevalence of adverse pregnancy outcome in neighbourhoods in the lowest tertile of socioeconomic status indicators, but there was no consistent trend in $PM_{2.5}$ exposure in relation to socioeconomic status: there was no trend in $PM_{2.5}$ exposure by tertile of percent unemployed; $PM_{2.5}$ exposure was higher in the highest tertile of percent low income; and there was a trend of higher $PM_{2.5}$ exposure with increasing percent of females who completed post-secondary education. Gradients in neighbourhood socioeconomic status variables were consistent with those in individual level maternal education in Quebec where individual level data on maternal education were available, i.e. compared to mothers with lower educational attainment, a larger percentage of mothers with higher educational attainment lived in DAs with: the highest percentage of females who had completed post-secondary education, the lowest percentage of individuals in the lowest income quintile, and the lowest percentage of unemployed individuals. Conversely, compared to mothers with higher educational attainment, a larger percentage of mothers with lower educational attainment lived in DAs with: the lowest percentage of females who had completed post-secondary education, the highest percentage of individuals in the lowest income quintile, and the highest percentage of unemployed individuals (see Supplemental Material, Table S3a-c).

Associations between $PM_{2.5}$ and pregnancy outcomes based on exposures averaged over the entire pregnancy are shown in Table 3, by level of adjustment for covariates. $PM_{2.5}$ exhibited a significant negative association with preterm birth in both unadjusted and fully adjusted models. SGA and term LBW exhibited significant positive associations, and term birth weight a significant negative association with $PM_{2.5}$ in unadjusted models. Associations of $PM_{2.5}$ with LBW, SGA and birth weight were not sensitive to adjustment for neighbourhood socioeconomic status, however they were all reduced substantially after adjustment for infant and maternal characteristics. Analysis by exposure period (Figure 1) revealed significant negative associations between $PM_{2.5}$ and preterm birth for all exposure periods except months 2 and 3, neither of which were significant. Associations with term LBW were consistently null over all exposure periods. Late pregnancy exposures appeared to exhibit stronger associations with SGA and term birth weight. There was a very large but imprecise estimated reduction in birth weight (10 μg/m^3 increase associated with reduction of -46.3 g, 95% CI -74.6, -18.0) for a small number of births (22,805) with gestational age greater than 9 months. We did not include this in the figure because it obscured the results for all other exposure periods. The association with term birth weight based on exposure over the entire pregnancy was not sensitive to exclusion of these births (-21.4 g, 95% CI -25.6, -17.1 vs. -20.5 g, 95% CI -24.7, -16.4 includimg these births).

We also conducted sensitivity analyses employing data from ground-based monitors for 24 cities (see Supplemental Material, Table S4) based on 1,140,920 singleton live births, and employing data from Quebec only (n=681,915 singleton live births), where we were able to adjust for individual level maternal education as a covariate. Significant negative associations were observed with preterm birth in both instances (Table 2), which were larger in magnitude than those observed in the full dataset, while associations with term LBW were null. Significant negative associations were observed with term birth weight, and a positive, non-significant association was observed with SGA in Quebec. These associations were comparable in magnitude to those observed in the full dataset.

Table 4 summarizes associations stratified by maternal place of birth, urban/rural place of residence, neighbourhood socioeconomic status, and time period. For SGA there was a significant positive association among mothers born in Canada, but no association among mothers born elsewhere. Associations with term birth weight were negative for both groups, but the estimated association was stronger for mothers born in Canada.A non-significant positive association was observed with preterm birth in the 1999-2003 period, whereas there was a significant negative association during the 2004-2008 period.The association with LBW was negative and non-significant in 1999-2003 and positive and non-significant in 2004-2008. Significant negative associations were observed for term birth weight in both periods, but the magnitude of the association was larger in the 2004-2008 period.

Discussion

We employed estimates of $PM_{2.5}$ exposure from a national spatiotemporal model in order to examine associations with preterm birth and term birth weight, low birth weight and small for gestational age in Canada between 1999 and 2008. Associations between $PM_{2.5}$ and pregnancy outcomes were sensitive to adjustment for individual covariates, but not neighbourhood socioeconomic status. In fully adjusted models, a 10 $\mu g/m^3$ increase in $PM_{2.5}$ over the entire pregnancy was associated with SGA (OR = 1.04, 95%CI 1.01, 1.07) and reduced term birth weight (-20.5 g, 95%CI -24.7, -16.4). Expressed per interquartile range (3.58 $\mu g/m^3$) increase, these values are 1.014 (95% CI 1.003,1.026) and -7.4 g (95% CI -8.9, -5.9).

To our knowledge only three previous studies have employed model/satellite-based estimates of $PM_{2.5}$ exposure to examine pregnancy outcomes in large studies examining both urban and rural areas. Kloog et al. (2012) reported that a 10 $\mu g/m^3$ increase in $PM_{2.5}$ was associated with a decrease in term birth weight of -13.8 g (95% CI -21.10, -6.05) and an odds ratio for preterm birth of 1.06 (95% CI 1.01, 1.13) from a study in Massachusetts, adjusting for infant and maternal characteristics including smoking. They found a positive, significant association with preterm birth based on entire pregnancy exposure, and a null association based on exposure during the last month. Hyder et al. (2014) estimated somewhat stronger associations except for preterm birth in a study in Connecticut and Massachusetts, also based on entire pregnancy exposure. They estimated that a 10 μg/m^3 increase in $PM_{2.5}$ was associated with decreases in birth weight ranging from -24.9 g (95% CI -33.2, -20.8) to -78.8 g (95% CI -95.4, -62.2) depending on the method of exposure assignment, odds ratios for term LBW ranging from 1.04 (95% CI 0.92, 1.18) to 1.38 (95% CI 1.04, 1.85), for SGA ranging from 1.13 (95% CI 1.04, 1.18) to 1.38 (95% CI 1.18, 1.54) and for preterm birth ranging from 1.00 (95% CI 0.96, 1.09) to 0.96 (95% CI 0.81, 1.13). Associations were adjusted for infant and maternal characteristics (including smoking) and were consistently larger based on satellite-derived exposures compared to those based on ground based monitoring, with the exception of associations with preterm birth which were consistently null. Greater exposure misclassification using ground based monitoring vs. satellite observations was identified as a possible explanation. Fleischer et al. (2014) reported a study of the association of satellite based estimates of $PM_{2.5}$ and preterm birth and LBW (all gestational ages) using the WHO Global Survey on Maternal and Perinatal Health in Africa, Asia and Latin America. $PM_{2.5}$ was not associated with either preterm birth or LBW across the entire sample, but the highest quartiles of exposure were associated with LBW, and in China, the highest quartiles were associated with both preterm birth and LBW. Maternal smoking data were not available in this study.

Our results are consistent with those observed in a recent meta-analysis (Stieb et al. 2012), as well as a multi-centre coordinated analysis (Dadvand et al. 2013). Based on a meta-analysis of case-control and cohort studies, Stieb et al. (2012) reported that a 10 μg/m^3 increase in $PM_{2.5}$ averaged over the entire pregnancy was associated with a summary odds ratio of 1.05 (95% CI 0.99, 1.12) for low birth weight (n=6 studies including studies of term LBW and all gestational age LBW) as well as a summary -23.4 g (95% CI -45.5, -1.4) reduction in birth weight (n=7 studies including studies of term LBW and all gestational age LBW) . An increase of 10 μg/m^3 $PM_{2.5}$ averaged over the entire pregnancy was also associated with a summary odds ratio of 1.16 (95% CI 1.07, 1.26) for preterm birth (n=4 studies). Dadvand et al. (2013) reported that an increase of 10 μg/m^3 $PM_{2.5}$ was associated with an odds ratio of 1.04 (95% CI 0.99, 1.09) for LBW and an -8.9 g reduction in birth weight (95% CI: -13.2, -4.6). They also found that associations were sensitive to adjustment for socioeconomic status and maternal and infant characteristics.

Subgroup analyses in our study revealed that associations varied across subgroups based on maternal place of birth, and time period. For SGA there was a significant positive association among mothers born in Canada, but no association among mothers born elsewhere. Associations with term birth weight were negative for both groups, but the estimated association was stronger for mothers born in Canada. Factors accounting for greater vulnerability to effects of $PM_{2.5}$ on risk of adverse pregnancy outcomes in population subgroups remain to be identified. Most other studies have examined effect modification by race rather than maternal place of birth, and results have been inconsistent (Bell et al. 2007; Morello-Frosch et al. 2010). A "healthy immigrant effect" has been suggested where recent immigrants experience better health and have better health behaviours (Ali et al. 2004). In our study, however, both $PM_{2.5}$ exposure and prevalence of LBW and SGA were higher among non Canadian born mothers. Our observation of a weaker association for births to mothers not born in Canada would suggest greater "resistance" to the incremental effect of air pollution on these outcomes in this population, but this would need to be replicated in other studies. It has been suggested that lower socioeconomic status confers a "double jeopardy" of increased stressors and increased exposure to environmental contaminants (Morello-Frosch et al. 2006). Woodruff et al. (2003) reported disparities in air pollution exposure during pregnancy based on a multi-pollutant index by race but not educational attainment in the US, while Buzzelli and Jerrett (2007) in a study in Toronto found higher NO_2 exposures among both those with lower incomes but also higher status occupations. We found similarly opposing trends in that $PM_{2.5}$ exposure was higher in the highest tertile of percent low income, but there was also a trend of higher $PM_{2.5}$ exposure with increasing percent of females who completed post-secondary education. Findings regarding effect modification by socioeconomic status in other studies have been mixed (Morello-Frosch et al. 2010; Ponce et al 2005; Yi et al. 2010). In particular, in a study in Montreal, Genereux et al. (2008) found that associations between proximity to highways and pregnancy outcome were only observed among high socioeconomic status mothers.We observed a non-significant positive association with preterm birth in the 1999-2003 period, and a significant negative association in the 2004-2009 period, as well as significant negative associations with birth weight in both periods. $PM_{2.5}$ concentrations declined between 1999 and 2008, while the prevalence of pregnancy outcomes did not exhibit a clear trend. Factors which could account for a change in risk associated with $PM_{2.5}$ over time, particularly in the opposite direction for preterm birth and birth weight outcomes, require further exploration.

We found that estimated maternal exposures for the entire pregnancy were highly correlated with those for trimester and month of gestation, making it difficult to uniquely identify critical exposure windows. Nonetheless, for SGA and term birth weight, we found that late pregnancy exposures exhibited the largest associations. Consistent negative associations were observed between preterm birth and $PM_{2.5}$ in most exposure periods. We do not consider it biologically plausible that air pollution exposure would have a protective effect with respect to preterm birth and hypothesize that this may reflect bias or residual confounding. Results in previous studies have been mixed, although in a recent meta-analysis a significant summary odds ratio greater than one was reported for $PM_{2.5}$ and preterm birth (n= 4 primary studies), and a non-significant summary odds ratio greater than one was reported for PM_{10} and preterm birth (n=3 primary studies), both based on entire pregnancy exposure (Stieb et al. 2012). Results for individual trimesters were variable, including summary odds ratios greater than and less than one, significant and non-significant (Stieb et al. 2012). In contrast, summary odds ratios for LBW were consistently greater than one, and summary estimates of changes in birth weight were consistently negative across individual trimesters and entire pregnancy exposure, although their magnitude was larger based on entire pregnancy exposure (Stieb et al.

2012). The latter finding could be partly attributable to a scaling effect in that there tends to be less variability in exposures over the entire pregnancy than in shorter gestational periods, as we observed. Additional analysis of preterm birth examining effects of exposure in the days or weeks preceding birth using time-series or case-crossover methods may be informative.

Strengths of our study include the very large sample size, availability of exposure estimates for births across the entire country, and evaluation of associations at comparatively low levels of exposure. To our knowledge, this is one of the largest reported analyses of air pollution and pregnancy outcomes, nearly as large as the entire pooled ICAPPO multi-centre study (Dadvand et al. 2013). The availability of exposure estimates from a nationally comprehensive model allowed us to include rural areas which would be excluded from studies relying on ground based monitoring networks. Mean levels of $PM_{2.5}$ exposure in our study were substantially lower than all centres included in the ICAPPO analysis other than Vancouver, allowing us to evaluate whether associations could be detected at low levels of exposure.

The study also has several limitations. We lacked data on potentially important confounding factors such as maternal smoking and alcohol use. However, it has been reported that associations between air pollution and preterm birth were not sensitive to adjustment for these factors in a case-control study of a approximately 2,500 births (nested within a cohort of approximately 60,000) in 2003 in Los Angeles County (Ritz et al. 2007). In a national U.S. study of infant mortality based on approximately 2.5 million births between 1999 and 2002, associations with air pollution (including $PM_{2.5}$) were not sensitive to adjustment for maternal smoking (Darrow et al. 2006). Villeneuve et al. (2011) reported that remote sensing based estimates of $PM_{2.5}$ exposure were negatively associated with smoking prevalence both in Ontario alone and in the rest of Canada, resulting in negative confounding of the association between $PM_{2.5}$ and lung cancer and heart disease mortality (i.e. increased magnitude of association with $PM_{2.5}$ after adjustment for smoking) . They proposed a method for upward adjustment of air pollution relative risks derived from studies lacking individual data on smoking. Smoking during pregnancy was also strongly associated with maternal education in Quebec (Gilbert et al. 2014) and neighbourhood socioeconomic status in Alberta (Wood et al. 2014), thus including socioeconomic status variables as covariates may partially account for effects of smoking. We employed neighbourhood level data on socioeconomic status. Luo et al. (2006), using data from Quebec, reported that individual measures of socioeconomic status (maternal education) and neighbourhood socioeconomic status (low income) were independently associated with risk of preterm birth and SGA, although associations of individual level maternal education were larger. Results of our sensitivity analysis using data from Quebec only where we were able to adjust for individual level maternal education, were consistent with national findings, suggesting that adjusting for neighbourhood SES adequately controlled for confounding by SES.

Conclusions

This study based on approximately 3 million births across Canada and employing $PM_{2.5}$ estimates from a national spatiotemporal model provides further evidence linking $PM_{2.5}$ and pregnancy outcomes. Associations between $PM_{2.5}$ and pregnancy outcomes were sensitive to adjustment for individual covariates, but not neighbourhood socioeconomic status. In fully adjusted models $PM_{2.5}$ was associated with SGA and term birth weight. These associations varied across subgroups based on maternal place of birth and time period . Further study to identify population groups at greater risk and to examine mechanisms which could account for increased vulnerability would be desirable.

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Table 1. Summary of estimated $PM_{2.5}$ exposures by exposure period ($\mu g/m^3$).

Period	N	Mean	Standard Deviation	5th Percentile	Median	95th Percentile	Interquartile Range
Entire pregnancy	2,966,705	8.43	2.40	4.61	8.44	12.42	3.58
Trimester 1	2,966,700	8.50	2.78	4.29	8.36	13.20	4.01
Trimester 2	2,966,705	8.44	2.77	4.26	8.30	13.14	3.99
Trimester 3	2,954,665	8.36	2.75	4.22	8.21	13.00	3.95
Month 1	2,966,695	8.51	3.11	4.08	8.20	13.89	4.35
Month 2	2,966,695	8.50	3.11	4.08	8.18	13.88	4.33
Month 3	2,966,700	8.48	3.11	4.06	8.17	13.87	4.34
Month 4	2,966,700	8.47	3.11	4.05	8.15	13.84	4.32
Month 5	2,966,700	8.45	3.10	4.04	8.13	13.81	4.31
Month 6	2,960,860	8.42	3.09	4.02	8.10	13.75	4.30
Month 7	2,951,295	8.39	3.09	4.01	8.06	13.71	4.28
Month 8	2,900,745	8.37	3.08	4.00	8.03	13.70	4.26
Month 9	2,086,560	8.33	3.08	3.98	7.99	13.66	4.27

Table 2. Prevalence of pregnancy outcomes and mean $PM_{2.5}$ exposures over the entire pregnancy by infant, maternal and neighbourhood characteristics.

Variable	Preterm birth n (%)	Term low birth weight n (%)	Small for gestational age n (%)	Mean $PM_{2.5}$ ($\mu g/m^3$)
Sex				
male	101,495 (6.67)	17,925 (1.26)	129,525 (8.51)	8.4
female	83,270 (5.77)	25,640 (1.88)	117,030 (8.11)	8.4
unknown	NR[a]	0 (0.0)	0 (0.0)	8.4
Maternal age				
<18	3,190 (8.08)	700 (1.93)	3,850 (9.76)	7.6
18 – 29	105,190 (6.13)	25,810 (1.60)	149,705 (8.73)	8.3
30 – 39	72,125 (6.20)	16,015 (1.47)	88,390 (7.60)	8.6
40+	4,240 (8.72)	1,035 (2.33)	4,595 (9.46)	8.7
unknown	20 (11.76)	NR	15 (8.82)	8.8
Marital status				
Single	53,960 (6.98)	13,150 (1.83)	71,900 (9.30)	8.2
Married	105,620 (5.70)	24,685 (1.41)	143,540 (7.74)	8.5
Widowed	190 (8.09)	40 (1.85)	220 (9.38)	8.8
Divorced	2,505 (7.54)	575 (1.87)	3,000 (9.03)	8.2
Separated	970 (8.51)	215 (2.06)	1,050 (9.21)	7.0
unknown	21,520 (7.37)	4,900 (1.81)	26,845 (9.20)	8.4
Maternal place of birth				
Canadian born	136,690 (6.26)	28,420 (1.39)	161,465 (7.39)	8.1
not Canadian born	44,920 (6.08)	14,370 (2.07)	80,835 (10.95)	9.4
unknown	3,155 (7.26)	775 (1.92)	4,255 (9.80)	10.3
Maternal place of residence				
urban	152,035 (6.24)	36,930 (1.62)	208,610 (8.57)	8.8
rural	32,730 (6.15)	6,635 (1.33)	37,945 (7.14)	6.6
Parity				
1st birth	91,230 (6.91)	23,765 (1.93)	139,055 (10.54)	8.5
2nd birth	54,345 (5.26)	11,870 (1.21)	66,940 (6.48)	8.5
3rd or greater birth	38,085 (6.39)	7,680 (1.38)	39,195 (6.58)	8.2
unknown	1,105 (6.30)	250 (1.52)	1,365 (7.79)	6.3
Maternal province of residence				
Newfoundland and Labrador	2,760 (6.77)	490 (1.29)	2,775 (6.81)	5.0
Prince Edward Island	640 (5.18)	140 (1.20)	840 (6.80)	5.3
Nova Scotia	4,705 (6.19)	1,135 (1.59)	6,165 (8.12)	6.1
New Brunswick	3,850 (6.10)	795 (1.34)	4,765 (7.56)	5.4
Quebec	42,715 (6.26)	9,815 (1.54)	55,825 (8.19)	9.5
Ontario	67,715 (6.01)	18,100 (1.71)	98,670 (8.76)	9.6
Manitoba	8,465 (6.66)	1,610 (1.36)	9,740 (7.67)	6.2

Variable	Preterm birth n (%)	Term low birth weight n (%)	Small for gestational age n (%)	Mean $PM_{2.5}$ ($\mu g/m^3$)
Saskatchewan	6,320 (6.05)	1,405 (1.43)	7,795 (7.46)	6.2
Alberta	26,070 (7.05)	5,505 (1.60)	32,000 (8.66)	7.9
British Columbia	21,465 (5.90)	4,560 (1.33)	27,930 (7.68)	6.5
Yukon	15 (11.11)	NR	5 (3.85)	5.2
N.W.T	20 (6.45)	NR	20 (6.45)	3.9
Nunavut	20 (11.11)	10 (6.25)	25 (14.29)	5.9
unknown	5 (33.33)	0 (0.00)	NR	7.9
Birth year				
1999	3,125 (6.45)	710 (1.57)	4,245 (8.77)	8.8
2000	19,340 (6.20)	4,410 (1.51)	25,375 (8.14)	9.0
2001	18,995 (5.97)	4,610 (1.54)	26,465 (8.33)	8.9
2002	18,745 (6.00)	4,580 (1.56)	26,000 (8.33)	8.8
2003	17,185 (6.2)	4,080 (1.57)	23,135 (8.35)	9.1
2004	20,305 (6.39)	4,615 (1.55)	25,770 (8.12)	8.5
2005	20,695 (6.30)	4,820 (1.57)	27,525 (8.39)	8.6
2006	21,620 (6.36)	5,245 (1.65)	28,905 (8.51)	8.2
2007	21,740 (6.20)	5,175 (1.57)	29,615 (8.46)	7.5
2008	23,015 (6.35)	5,320 (1.57)	29,520 (8.14)	7.6
1999-2003	77,390 (6.10)	18,390 (1.54)	103,220 (8.3)	8.95
2004-2008	107,375 (6.32)	25,175 (1.58)	141,335 (8.32)	8.05
Season				
Spring	46,690 (6.18)	10,550 (1.49)	60,355 (8.00)	8.1
Summer	45,980 (6.02)	11,220 (1.56)	64,170 (8.40)	8.6
Fall	47,010 (6.35)	11,195 (1.61)	63,140 (8.53)	8.4
Winter	45,085 (6.38)	10,600 (1.60)	58,895 (8.34)	8.7
Percent unemployed (age 15+)				
1st tertile (≤4.6%)	58,785 (5.98)	13,020 (1.41)	75,945 (7.72)	8.4
2nd tertile (4.61-8.22%)	60,380 (6.14)	14,255 (1.54)	81,180 (8.26)	8.5
3rd tertile (>8.22%)	64,810 (6.56)	16,120 (1.75)	88,535 (8.97)	8.4
Unknown	790 (6.55)	170 (1.51)	900 (7.47)	7.9
Percent in lowest income quintile (age 15+)				
1st tertile (≤9.25%)	57,235 (5.82)	11,890 (1.28)	70,080 (7.12)	8.2
2nd tertile (9.26-20.18%)	59,970 (6.10)	13,970 (1.51)	80,320 (8.17)	8.3
3rd tertile (>20.18%)	66,770 (6.76)	17,530 (1.90)	95,260 (9.65)	8.8
Unknown	790 (6.55)	175 (1.55)	895 (7.43)	7.9
Percent of females completed postsecondary education (age 25+)				
1st tertile (≤20.36%)	65,585 (6.66)	15,900 (1.73)	86,385 (8.78)	8.1
2nd tertile (20.37-28.47%)	61,085 (6.21)	14,610 (1.58)	82,850 (8.42)	8.5
3rd tertile (>28.47%)	57,305 (5.81)	12,885 (1.39)	76,425 (7.75)	8.8
Unknown	790 (6.55)	170 (1.51)	895 (7.43)	7.9

Variable	**Preterm birth n (%)**	**Term low birth weight n (%)**	**Small for gestational age n (%)**	**Mean $PM_{2.5}$ (μg/m^3)**
Percent visible minority				
1st tertile (≤2.04%)	60,480 (6.20)	12,575 (1.37)	71,415 (7.33)	7.3
2nd tertile (2.05-16.13%)	59,685 (6.08)	12,745 (1.38)	74,640 (7.60)	8.6
3rd tertile (>16.13%)	62,640 (6.39)	17,825 (1.94)	98,260 (10.03)	9.4
Missing	1,960 (6.75)	415 (1.53)	2,240 (7.72)	7.3
Total	184,765 (6.23)	43,560 (1.57)	246,555 (8.31)	8.4

[a]Not reported. In accordance with Statistics Canada disclosure rules, case counts of less than five were suppressed, and all frequencies were randomly rounded to base five. Statistical analyses employed unrounded data.

Table 3. Associations between $PM_{2.5}$ over the entire pregnancy and pregnancy outcome, by level of adjustment (per 10 μg/m^3).

Model	**Preterm birth Odds Ratio (95% confidence interval)**	**Term low birth weight Odds Ratio (95% confidence interval)**	**Small for gestational age Odds Ratio (95% confidence interval)**	**Term birth weight β (95% confidence interval)**
unadjusted	0.96 (0.93, 0.98)	1.51 (1.44, 1.57)	1.46 (1.43, 1.49)	-115.5 (-119.7, -111.3)
+ neighbourhood SES[a]	0.97 (0.95, 1.00)	1.47 (1.41, 1.54)	1.41 (1.38, 1.44)	-107.3 (-111.6, -103.0)
+ individual covariates[b], neighbourhood percent visible minority (fully adjusted))	0.96 (0.93, 0.99)	1.01 (0.94, 1.08)	1.04 (1.01, 1.07)	-20.5 (-24.7, -16.4)
24 Cities (fully adjusted)	0.80 (0.75, 0.86)	0.98 (0.87, 1.10)	0.99 (0.93, 1.04)	-20.2 (-27.7, -12.6)
Quebec (fully adjusted)	0.90 (0.84, 0.96)	0.98 (0.86, 1.12)	1.03 (0.97, 1.09)	-16.1 (-26.5, -5.7)

[a]Socioeconomic status; census dissemination area proportion of individuals 15 and over who were unemployed (preterm birth model only), proportion of individuals 15 and over in the lowest income quintile, and proportion of females 25 and over with post-secondary education; [b]Maternal age and marital status, parity, urban/ rural place of residence, airshed of maternal place of residence, place of birth of mother (within/outside Canada), year of birth, season of birth and proportion of census dissemination area population who are visible minority; infant sex was also included in preterm birth, LBW and birth weight models, and gestational age was also included in LBW and birth weight models.

Table 4. Associations between $PM_{2.5}$ over the entire pregnancy and pregnancy outcome, by maternal place of birth, urban/rural place of residence, neighbourhood socioeconomic status and time period, in models adjusted for neighbourhood socioeconomic status and individual covariates (per 10 μg/m^3).

Interaction	**Preterm birth Odds Ratio (95% confidence interval)**	**Term low birth weight Odds Ratio (95% confidence interval)**	**Small for gestational age Odds Ratio (95% confidence interval)**	**Term birth weight β (95% confidence interval)**
Maternal place of birth				
Canada	0.94 (0.91, 0.98)	1.04 (0.96, 1.13)	1.09 (1.05, 1.13)	-30.9 (-35.6, -26.1)
Elsewhere	0.95 (0.88, 1.03)	0.97 (0.85, 1.11)	0.97 (0.92, 1.04)	-10.1 (-18.6, -1.6)
p-value	0.81	0.38	0.0014	<0.0001
Maternal place of residence				
Urban	0.96 (0.92, 1.00)	1.00 (0.93, 1.08)	1.02 (0.99, 1.06)	-15.8 (-20.3, -11.3)
Rural	0.96 (0.88, 1.05)	0.97 (0.81, 1.17)	1.05 (0.97, 1.14)	-21.1 (-31.4, -10.9)
p-value	1.00	0.76	0.52	0.35
Percent in lowest income quintile (age 15+)				
1st tertile (≤9.25%)	0.92 (0.87, 0.98)	1.00 (0.88, 1.13)	1.02 (0.97, 1.08)	-17.8 (-24.2, -11.5)
2nd tertile (9.26-20.18%)	0.97 (0.91, 1.03)	0.92 (0.82, 1.04)	1.03 (0.97, 1.08)	-12.6 (-19.2, -6.1)
3rd tertile (>20.18%)	0.97 (0.91, 1.03)	1.00 (0.89, 1.12)	0.98 (0.92, 1.03)	-9.4 (-17.8, -1.1)
p-value	0.37	0.53	0.42	0.26
Period				
1999-2003	1.05 (0.99, 1.11)	0.89 (0.80, 1.00)	1.03 (0.98, 1.08)	-12.5 (-18.6, -6.4)
2004-2008	0.90 (0.85, 0.94)	1.09 (0.99, 1.19)	1.05 (1.01, 1.10)	-28.7 (-34.0, -23.4)
p-value	<0.0001	0.006	0.56	<0.0001

Figure Legend

Figure 1. Associations of $PM_{2.5}$ with pregnancy outcomes by exposure period. (Estimated using generalized estimating equations accounting for clustering of observations by census dissemination area and adjusting for census dissemination area proportion of individuals 15 and over who were unemployed (preterm birth model only), proportion of individuals 15 and over in the lowest income quintile, and proportion of females 25 and over with post-secondary education, maternal age and marital status, parity, urban/ rural place of residence, airshed of maternal place of residence, place of birth of mother (within/outside Canada), year of birth, season of birth and proportion of census dissemination area population who are visible minority; infant sex was also included in preterm birth, LBW and birth weight models, and gestational age was also included in LBW and birth weight models. An estimate is not provided for preterm birth and exposure during the 9th month of gestation because only non-cases would have been exposed during this time period.)

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Figure 1.